

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER

CORRESPONDENCE



CIRCA PHARMACEUTICALS, INC.

33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
(516) 842-8383 FAX (516) 842-8630

Fax transmitted from (516) 842-6638

FAX TRANSMISSION

Date: January 29, 1999

To: Radhika Rajagopalan

From: Joyce A. DelGaudio

Fax #: 301-443-3839

Total number of pages including this cover page: 10

MESSAGE

As per our telephone discussion, please find attached the
Telephone Amendment for Nicotine Polacrilex Gum, 4 mg
ANDA 74-707.

Thank you.

If you do not receive all pages or have any problems with receiving this transmission, please call (516) 842-8383, extension 241.

CONFIDENTIALITY NOTE

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CIRCA PHARMACEUTICALS, INC.

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January 29, 1999

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
Room 204, HFD 637
7500 Standish Place
Rockville, MD 20855

**RE: Nicotine Polacrilex Gum, 4 mg; ANDA 74-707
TELEPHONE AMENDMENT**

Dear Mr. Sporn:

Reference is made to our above mentioned Abbreviated New Drug Application dated July 6, 1995. Reference is also made to a telephone conversation between Radhika Rajagopalan, Chemistry Reviewer, and myself, dated January 28, 1999.

Dr. Rajagopalan contacted Circa in order to request that we include a blister seal integrity test during our stability studies of the drug product that is the subject of this ANDA. She referred to the request made by Dr. Florence Fang, Tertiary Reviewer, Office of Generic Drugs in regard to our nicotine polacrilex gum, 2 mg ANDA,

Dr. Fang had contacted Circa on October 7, 1998 in order to request that we include a blister seal integrity test during our stability studies of this drug product. After careful consideration of this request, Circa contacted Dr. Fang (October 30, 1998) and informed her that the gum product identity, strength, quality and purity will be assured by the current stability specifications, which include potency assay, chromatographic purity and description/appearance. Therefore, we do not feel that the addition of a seal integrity test and specification for which we have no data on which to set a reasonable limit, would yield additional information about this drug product.

However, given the suggestion of Dr. Fang, Circa committed to include a leak test in the post approval stability program for the 2 mg. In this regard, in response to Dr. Rajagopalan's request, we will also commit to include a leak test in the post approval stability program for this product (first three commercial batches and annual batch thereafter). The method of test will be the vacuum/liquid procedure that is commonly used in industry for in-process checks during a blister packaging run. As stated previously, we have no data on which to base a reasonable specification, therefore, at this time, the specification will state "Report Results". When a database has been established, Circa will evaluate the results, and decide what, if any, specification must be set. The ANDA will be supplemented as appropriate at that time.



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January 29, 1999
Page 2

Dr. Fang had also requested that we report any failures of this leak test to the FDA at the stability timepoint they are discovered, rather than wait until the annual report. While Circa will agree to this request, we would like to reiterate that we are reporting these results, and that there is no specification. Any failure in the leak test will be reviewed in conjunction with our assay, chromatographic purity and description/appearance tests. Should our chemistry analysis be within specification, the relevance of the leak test will be discussed with your office.

Thank you for your prompt review of this information. If there are any questions or problems, please do not hesitate to contact us immediately.

Pursuant to 21 CFR 314.96(b), we certify that a true field copy of this amendment has been sent by overnight courier to: Ms. Brenda Holman, District Director, FDA (NYK-DO), 850 Third Avenue, Brooklyn, NY 11232-1593.

Sincerely,
CIRCA PHARMACEUTICALS, INC.

A handwritten signature in cursive script, reading "Joyce Anne DelGaudio".

Joyce Anne DelGaudio
Director, Regulatory Affairs



CIRCA PHARMACEUTICALS, INC.

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January 29, 1999

Archival Copy

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
Room 204, HFD 637
7500 Standish Place
Rockville, MD 20855

NDA ORIG AMENDMENT

N/AC

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TELEPHONE AMENDMENT**

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January 29, 1999
Page 2

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Sincerely,
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A handwritten signature in cursive script, reading "Joyce Anne DelGaudio".

Joyce Anne DelGaudio
Director, Regulatory Affairs



CIRCA PHARMACEUTICALS, INC.

33 RALPH AVENUE P.O. BOX 30 COPIAGUE, NY 11726-0030
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September 2, 1998

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
Room 204, HFD 637
7500 Standish Place
Rockville, MD 20855

Archival Copy

*Labeling
Review Drafted
11/25/98
LW*

NDA ORIG AMENDMENT

N/A

RE: **Nicotine Polacrilex Gum, 4 mg ANDA 74-707**
MAJOR AMENDMENT

Dear Mr. Sporn:

We refer to the April 20, 1998 facsimile letter (copy attached) from the Division of Chemistry II providing CMC comments, and the Division of Labeling and Program Support, providing labeling comments, on the August 14, 1997 amendment to our Abbreviated New Drug Application. The ANDA was originally submitted on July 6, 1995 pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum, 4 mg.

The following is an item-by-item response to the deficiencies noted in the letter:

Chemistry Deficiencies:

1. *Since the master batch records have gone through significant changes we request you provide a new reprocessing statement.*

Response: A new reprocessing statement is enclosed under Attachment 1.

2. *We notice your response to questions 6.b and 6.c. The gum release sample or the bulk finished product sample subjected to potency testing is not the intent of question 6.b. Since you intend to manufacture at least 18 loads per day, blend uniformity of these loads is requested. Content uniformity testing on individual mixing loads needs to be performed to ensure blend uniformity. Please provide a commitment to testing for blend uniformity on individual sub-batches.*

[Handwritten signature]

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ANDA 74-707
September 2, 1998
Page 2

Response: It is Circa's intention to conduct extensive testing on mixer loads on the first validation batches as per an approved validation protocol, in order to prove the homogeneity of the mix. This will be done by sampling a gum mass from the of every an of gum from a particular -batch (not less than samples, which is representative of the entire sub-batch [mixer load]). In order to confirm routine blend uniformity after the mixing process has been validated, we commit to taking a blend sample from any position in the mixer, for each mixer load (individual sub-batch of for analysis.

3. *According to 21 CFR, all manufacturing operations are to be completed within 30 days (compounding to packaging in final form). What time delay do you anticipate between different manufacturing steps including bulk and blister packaging.*

Response: We have enclosed data that supports holding the product in bulk (prior to blister packaging), in either ums or s, for 90 days. As stated in our Master Batch Formula for Rolling and Scoring, at the completion of rolling and scoring, the gum pieces will be transferred to properly prepared (. They will then be packaged in sags for shipment to our contract blister packager. This will take place in as short a time span as possible. In support of this process, we placed Nicotine Polacrilex Gum, 4mg, Lot #RD1203 on warehouse stability in drums (double lined with), 12"x16" gs and 15"x21" for 1, 2 and 3 months. The stability summary sheets containing all data for this study are enclosed under Attachment 2.

4. *Please clarify at what stage you will issue a finished product COA. The gum pieces packaged in the g double configuration is (as you have indicated yourself) "Bulk Finished Product Release Samples" (Response 6.k.) Complete testing should be carried out after the product is packaged in its commercial form. Page 119 of the amendment indicates that complete testing is performed on the bulk product, but not on the finished packaged product. This is unacceptable. We request that you modify the specifications on page 168 to reflect complete testing and provide a COA for batch RD1203.*

Response: As per your comment, complete testing will be carried out after the product is packaged in its commercial form. In this regard, we have revised the finished product specifications and procedure to include the test for blister packaging identification. The specification and procedure, along with a COA for Lot #RD1203, which includes results for the product after it was packaged in the proposed commercial form, are included under Attachment 3.



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Page 3

5. *Please amend the ANDA with controlled room temperature (25 °C/60% RH) stability data gathered after 6 months (5/97).*

Response: The stability summary sheets for Nicotine Polacrilex Gum, Lot #RD1203 are enclosed under Attachment 4. Please note this includes accelerated data (40°C/75% RH) out to 24 weeks and controlled room temperature data (25°C/60% RH) out to 18 months.

Comment:

We request you to provide data as per the letter (dated 4/2/98) issued by the Division of Bioequivalence.

Response: We are currently preparing a response to the letter dated 4/2/98 from the Division of Bioequivalence.

Labeling Deficiencies:

1. *GENERAL COMMENTS*

- a. *We acknowledge your comment to differentiate your two products by the use of contrasting colors.*
- b. *We also acknowledge your submission of a study entitled "Smokers' Attitudes Toward and Preferences in Nicotine Gum". This study is currently under review. We will not comment on this study until its review is completed.*

2. *CONTAINER (Blister Pack)*

- a. *We note your comments concerning the child resistant nature of your container.*
- b. *We encourage the inclusion of "USP" in the established name.*

Response: We have revised our labeling for the blister pack as per FDA comment. We have also revised it as per comments made on the 2 mg product () in that we indicate that there are 4 mg of nicotine in the drug product [e.g., 4 mg (nicotine)].



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Page 4

Four copies of the revised draft, as well as a side-by-side comparison of the revised labeling compared to the previously submitted labeling, are enclosed under Attachment 5.

3. *CARTON (Starter and Refill)*

- a. *We acknowledge your commitments to make the revisions as stated in our letter of March 6, 1997.*
- b. *Front Panel – Add the statement “IF YOU SMOKE LESS: try Nicotine Polacrilex Gum, 2 mg” at the bottom immediately beneath the statement “FOR SMOKERS OVER 24 CIGARETTES A DAY” and on the same line as “108 chewing pieces”.*
- c. *Bottom Panel – Please submit pictorials as seen on Nicorette's bottom panel.*
- d. *Back Panel – See comment 4 © below.*

Response: We have revised the labeling for our starter and refill cartons as per FDA comment. In response to comment 3(d), please note that our support system contains reference to a toll free telephone number. We have not yet been assigned the toll free number, therefore, at this time, the number reads as 1-800-XXX-XXXX. When this number is assigned, the appropriate reference numbers will appear on the back panel. We have also revised this labeling as per comments made on the 2 mg product (A) in that we indicate that there are 4 mg of nicotine in the drug product [e.g., 4 mg (nicotine)], we have increased the prominence of the established name on the front panel and have included the strength (4 mg) on the right and left flap (starter carton only, as the established name does not appear on the left and right flaps of the refill carton).

Four copies of the revised draft, as well as a side-by-side comparison of the revised labeling compared to the previously submitted labeling, are enclosed under Attachment 6 (starter carton) and Attachment 7 (refill carton).

4. *USER'S GUIDE*

- a. *Will your User's Guide have pictures?*
- b. *Stickers – Please state (below the stickers) where the stickers are to be placed on the calendar, as does the reference listed drug.*



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Page 5

- c. *We acknowledge your comments regarding the page numbers and telephone numbers and that you are in the process of developing a support system. Please note that this information should also appear on the back panel of the carton labeling – See comment 3(d) above.*

Response: We have established the final design of our User's Guide, and have incorporated the changes requested in the comments above, including the use of pictures to emphasize the text message. The final design for the User's Guide also includes page numbers and the appropriate page references where applicable. We have also revised this labeling as per comments made on the 2 mg product (AND, in that we indicate that there are 4 mg of nicotine in the drug product [e.g., 4 mg (nicotine)]).

Four copies of the final design for the User's Guide, as well as a side-by-side comparison of the revised labeling compared to the previously submitted labeling are enclosed under Attachment 8. Please note that the side-by-side comparison has been done with the text version of the User's Guide rather than the final design version, for ease of review.

Additionally, the Support System has now been developed, and four copies of the draft are enclosed under Attachment 9. As stated previously, a final phone number has not been assigned, however, it will be a toll free number. Once the number has been finalized, it will appear on the back panel of the carton label, as well as in the User's Guide. The starter and refill carton have been revised to refer to this number.

5. *AUDIO TAPE*

The text for your proposed audio is not the same as that for the reference listed drug, Nicorette®. Please note that the text of the audiotape for Nicorette® was reviewed and approved by the Medical Review Officer in the appropriate review division. 21 CFR 314.94(a)(8)(iv) requires that your labeling be the same as the labeling approved for the reference listed drug except for the differences cited therein. Please revise your tape text to be in accord with that of Nicorette®.

Response: In response to your comment, our tape text has been revised to be in accord with that of Nicorette®. Four copies of the revised audio tape text, as well as side-by-side comparisons of the proposed labeling to our last submitted labeling, can be found under Attachment 10.



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Page 6

Since we are submitting draft labeling, we note that we will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, we are aware that color and other factors (print size and prominence, etc.) in final printed labeling could be found unacceptable and that further changes may be requested prior to approval.

We note and acknowledge that you reserve the right to request further changes in our labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Pursuant to 21 CFR 314.96(b), we certify that a true field copy of this amendment has been sent by overnight courier to:

Ms. Brenda Holman
District Director
FDA (NYK-DO)
850 Third Avenue
Brooklyn, NY 11232-1593

Sincerely,
CIRCA PHARMACEUTICALS, INC.

A handwritten signature in cursive script, reading "Joyce Anne DelGaudio".

Joyce Anne DelGaudio
Director, Regulatory Affairs



August 14, 1997

Archival Copy

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Metro Park North II
Room 204, HFD 637
7500 Standish Place
Rockville, MD 20855

AMENDMENT

RE: **Nicotine Polacrilex Gum, 4 mg ANDA 74-707**
MAJOR AMENDMENT

Dear Mr. Sporn:

We refer to the January 29, 1997 letter (copy attached) from the Division of Chemistry II providing comments on our Abbreviated New Drug Application dated July 6, 1995, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Nicotine Polacrilex Gum, 4 mg.

As stated in your letter, Circa has made minor changes in the formulation of the drug product to more closely match the flavor and color of the innovator, as well as improve the stability performance. Information regarding these changes was submitted in correspondence to this ANDA dated August 15, 1996 and October 18, 1996. Therefore, in addition to responding to the deficiencies in the above mentioned letter, pursuant to 21 CFR §314.96, we are now submitting the supporting data in this amendment to our ANDA, which provides for the change in the formulation of our drug product to more closely mimic the flavor of the innovator, and provides assurance that our product will remain stable through its proposed expiration dating period of 24 months.

We have manufactured a new batch of nicotine polacrilex gum, 4 mg, Lot #1203, according to the revised formulation contained in this amendment. This lot has been blister packaged in a configuration with PVC as the product contact surface, and placed on stability. The data generated from this new lot of drug product is presented in this amendment, therefore, our response will address only those deficiencies that are pertinent to this modified formulation and the above mentioned packaging configuration.

Pursuant to 21 CFR 314.96(b), we certify that a true field copy of this amendment has been sent by overnight courier to: Brenda Holman, District Director, FDA (NYK-DO), 850 Third Avenue, Brooklyn, NY 11232-1593.

Sincerely,

Joyce Anne DelGaudio
Director, Regulatory Affairs

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AUG 15 1997

GENERIC DRUGS



ANDA 74-707
August 14, 1997
Page 2

RESPONSE

Details of the flavor and color change, as well as documentation in support of these revisions are included under Attachment 1 as follows:

- a) Overview
- b) Comparative Composition List (original formulation vs. revised formulation).
- c) Documentation for Nicotine Polacrilex Resin, USP (18% nicotine), Lot #4635, the lot of active pharmaceutical ingredient (API) used in Lot #RD1203 (ANDA support batch).
- d) Documentation for g Gum Flavor , used in Lot #RD1203.
- e) Documentation for Color Lake Blend Lot #3142, used in Lot #RD1203.
- f) Revised Master Batch Formula, Mixing Process
- g) Revised Master Batch Formula, Rolling and Scoring Process
- h) Executed batch records (mixing process) for reformulated nicotine polacrilex gum, 4 mg, Lot #'s RD1201 and RD1202
- i) Executed batch record (rolling and scoring process) for reformulated nicotine polacrilex gum, 4 mg, Lot #RD1203
- j) In-process QA data (weight and thickness checks) for Lot #RD1203
- k) Packaging Records for Lot #RD1203
- l) Analytical data for Lot #RD1203
- m) Stability data for Lot #RD1203
- n) Request for biowaiver with supporting data.

Page(s) 17

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry

Labeling Deficiencies:

1. GENERAL COMMENTS

- a. *Please submit draft OTC labeling to this application.*

Response: Draft OTC labeling for this drug product has been submitted under Attachment 14. This attachment contains four copies each of the draft labeling for the Starter Pack Carton, Refill Pack Carton, Patient Instruction Booklet and Audio Tape. We have also enclosed side-by-side comparisons of our labeling to the innovators, Nicorette® labeling.

- b. *We encourage the inclusion of "USP" in the established name for this drug product where it appears on your labels and labeling.*

Response: We have revised our labeling to include the USP designation in the established name where it appears on our labels and labeling.



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2. CONTAINER

- a. See GENERAL COMMENTS.
- b. *The innovator is required to market this product in a child-resistant blister. Please provide information regarding the child-resistant nature of your container.*

Response: The blister package that Circa will use for the marketed product is a paper backed foil that is sealed to the blister (PVC/PVDC) material. As stated in the instructions on our proposed labeling, to remove the gum the consumer must tear off a single unit. There is a corner on each individual piece that will have a loose edge. The paper backing is pulled off starting at this loose edge. The gum piece is then pushed through the foil. This is identical to the child resistant technology that the innovator is currently using.

3. CARTON

We encourage the use of boxing, contrasting colors, or other means to differentiate the strengths of this product from your proposed 2 mg strength product (ANDA

Response: A commitment is made to differentiate the two strengths with contrasting colors. This will be evident on our final printed labeling.

We note and acknowledge that you reserve the right to request further changes in our labels and/or labeling based upon further changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

Additional Comments and Acknowledgments

- 1. We have enclosed a copy of the "Consumer Research Preference Study" that was referenced in the August 15, 1996 correspondence. The report can be found under Attachment 15.
- 2. We acknowledge the fact that the Division of Bioequivalence must conduct a reevaluation of our application based on our request for a waiver from *in-vivo* bioequivalence studies for our reformulated drug product. The comparative analytical data in support of this waiver can be found under Attachment 1.n.